CENTER FOR VETERINARY MEDICINE
PROGRAM POLICY AND PROCEDURES MANUAL GUIDE 1243.3200

OFFICE OF NEW ANIMAL DRUG EVALUATION
REVIEWERS' CHAPTER

ROUTING A REQUEST TO OBTAIN A REVIEW OF AN INAD, JINAD, ANADA, NADA, OR VMF SUBMISSION

I. PURPOSE

This Guide describes the standard procedures for routing a request for a review of an Investigational New Animal Drug (INAD) file, a Generic New Animal Drug (JINAD) file, an Abbreviated New Animal Drug Application (ANADA), a New Animal Drug Application (NADA), or a Veterinary Master File (VMF) submission to a specialty division or team.

Responsible Office: ONADE Quality Assurance Team (HFV-102).
Date: 11/16/2001

II. REQUESTING A REVIEW

Following the determination that an application or submission is acceptable for review, the reviewer makes an assessment of what reviews are needed and routes the submission or pertinent parts of the submission to the appropriate team for review.

NOTE: Any primary reviewer (i.e., a reviewer in a Target Animal Division) may request a review from any specialist in the Center (e.g., target animal safety, human food safety, etc., or any specialty listed on the CVM Resource List). In addition, a reviewer in a specialty division may request a review (e.g., statistics, pharmacokinetics, Target Animal, etc.) from a primary reviewer. The submission should be sent to the appropriate Division or Team. The "Action Requested" section of the Review Request and Movement Form should clearly indicate what type of review is being requested so that it can be forwarded to the proper specialist.

III. GENERAL RULES GOVERNING A REQUEST FOR A REVIEW

The following guidelines concern requests for a specialty review:

A. The request for a specialty review is logged through the Document Control Unit (DCU) (HFV-103) using the Submission Tracking and Retrieval System (STARS).

B. The request for review is prepared within a few days of receipt. The requester should keep in mind the current ONADE timeframes for documents so that the reviewer receiving the request has adequate time to complete it. See CVM Policy and Procedures Guide (CVM P&P Guide) 1243.2580, Submission Document and Tracking, for information on timeframes.

C. The request for review is sent to the specific specialty division/team identified by the primary reviewer.

D. If a request for a review is sent incorrectly, the recipient team reroutes the request to the correct address through HFV-103, and informs the primary reviewer.

E. When the requested specialty review is completed, it is returned to the primary reviewer in paper (hard) copy and also in electronic format. Electronic format enables the efficient incorporation of the transmittal section into the letter to the sponsor.

F. The division/team that prepares the specialty review is responsible for ensuring that a copy is made available on the R: drive of the network.

IV. ROUTING A REQUEST FOR A CHEMISTRY, MANUFACTURING, AND CONTROLS REVIEW

A request for a Chemistry, Manufacturing, and Controls (CMC) review is routed to the appropriate Team in the Division of Manufacturing Technologies as follows:

A. If the application pertains to a sterile, biological/biotechnology, competitive exclusion, transgenic, or fermentation derived drug product, the submission is routed to the Antimicrobial Team (HFV-142).

B If the application pertains to a non-sterile drug product (i.e., tablets, solution, soluble powder, Type A medicated articles, etc.), the submission is routed to the Chemotherapeutics Team (HFV-143).

V. ROUTING A REQUEST FOR A HUMAN SAFETY REVIEW

If a drug is intended for use in food-producing animals, or if the submission contains user safety issues, the submission or pertinent parts are sent for review by the appropriate team in the Division of Human Food Safety (HFV-150). The team to which the request for review is routed depends on the type(s) of study(ies) in the submission:

A. If only **toxicology data** (e.g., general toxicology, genetic toxicology, and reproductive toxicology studies) are included in the package, the request is sent to the Toxicology Team (HFV-153).

B. If a submission has only **residue data** (e.g., studies and summaries of studies pertaining to presence and identification of residues in edible tissues, metabolism studies in the target species, comparative metabolism studies in the toxicological species, residue depletion studies in the food-producing animal, analytical methods for detection or identification of residues in the target animal), the request for review is sent to the Residue Chemistry Team (HFV-151).

C. If only **antimicrobial resistance data** (e.g., protocols, study reports, supporting literature, etc., pertaining to antimicrobial resistance of pathogen load) are included in the package, a request for review is sent to the Microbial Food Safety Team (HFV-157). All applications for new antimicrobials or changes to previously approved antimicrobial drugs should be routed to the Microbial Food Safety Team.

D. If a submission contains **user safety** data, then a review is sent to the Toxicology Team (HFV-153). The requestor should provide all available toxicology studies (e.g., acute eye irritation, skin irritation, etc.), user exposure information, and proposed user safety warning or precautionary statements for the product label.

E. If a submission contains data/studies applicable to more than one team in the Division of Human Food Safety (HFV-150), then a request for a review is sent to the Division of Human Food Safety for distribution to the appropriate reviewer(s) within the division. This includes slaughter authorizations.

VI. ROUTING A REQUEST FOR AN ENVIRONMENTAL REVIEW

All applications or petitions requesting agency action require the submission of an environmental assessment (EA) or a claim of categorical exclusion (21 CFR 25.15).

An INAD, JINAD, ANADA, or NADA submission may contain environmental study protocols, environmental study reports, an environmental assessment, or a claim for a categorical exclusion from preparing an EA.

A. If a submission contains environmental protocols, study reports, an EA or similar information, the submission is sent to the Environmental Assessment Team (HFV-145) for review.

B. If a submission contains a claim for categorical exclusion from preparing an EA, the submission is generally reviewed by the primary reviewer following the guidance contained in CVM Policy and Procedures Manual Guide 1243.7220, Environmental Review: Evaluating Claims of Categorical Exclusion for Actions Relating to New Animal Drugs.

C. If the primary reviewer determines that the claim for categorical exclusion requires review or concurrence by the Environmental Assessment Team, then the submission should be forwarded to HFV-145 for review.

VII. ROUTING A REQUEST FOR A STATISTICAL REVIEW

A. A request for a statistical review for an INAD, JINAD, ANADA, or NADA submission is routed to the Biometrics Team.

B. A statistical review differs from most other reviews because it is generally not intended as a stand-alone review. The Biometrics Team may provide a review on specific statistical aspects of a single study or an analysis of pooled studies. Prior to the statistical review, the primary reviewer of the submission should ensure that the study is generally acceptable, and that the measurements selected or proposed are appropriate.

NOTE: A specialty reviewer may also request a statistical review.

In practice, a copy of the submission is forwarded to the Biometrics Review Team (HFV-105) immediately (and placed in the queue). If the reviewer finds during the course of his review that the submission is not acceptable, he meets with the Biometrics reviewer to discuss whether the Biometrics review should continue. HFV-105 prepares a transmittal section and sends it to the requestor of the review. If a submission contains bioavailability and bioequivalence studies, it may be routed differently.

VIII. ROUTING A REQUEST FOR DIVISION OF HUMAN FOOD SAFETY CONCURRENCE ON FOI SUMMARY AND THE DRAFT REGULATION

A. Draft Approval Package:

If the approval is for a new drug intended for use in food-producing animals, the draft approval package requires a concurrence from the Division of Human Food Safety (HFV-150). Otherwise, the approval package is forwarded directly to the Quality Assurance Team (HFV-102) for review. The Division of Human Food Safety (HFS) verifies that the HFS section of the approval package is accurate and complete.

B. Final Approval Package:

The final approval package must also be sent to HFV-150 for final concurrence if:

- any changes are made to the HFS information in the components of the approval package during or after the draft approval process,
- changes were requested during the draft approval process, or
- the approval will result in a change to the human food safety regulation (21 CFR 556).

If not, the final approval package goes to HFV-102 through DCU and does not go to HFV-150 in final form.

NOTE: The movement of the draft and final approval packages is tracked with the STARS transmittal form called "Tracking Form for Approvals Requiring Administrative Review" (printed on yellow paper). This form is attached to ***Folder A*** of the approval package and the necessary concurrences are documented both on the transmittal form and the FOI Summary signature page.

IX. ROUTING A REQUEST FOR PREPARATION OF A DRAFT FEDERAL REGISTER DOCUMENT

The reviewer determines if the approval will result in a change to the regulations. Most approvals require preparation of a draft Federal Register document announcing approval of a New Animal Drug Application ("draft regulation"). Exceptions include most manufacturing supplements and some labeling changes.

The reviewer sends a request to the Policy and Regulations Team (HFV-6) to prepare a draft regulation. Refer to CVM P&P Guide 1240.3125 for preparation.

HFV-6 prepares the draft Federal Register document (draft regulation), assigns a Federal Register Document Tracking System (FRDTS) number, and works with the primary reviewer to ensure the draft regulation is accurate. Upon completion, HFV-6 forwards the draft regulation to the primary reviewer through the DCU.

X. ROUTING A REQUEST FOR AN ENVIRONMENTAL ASSESSMENT TEAM CONCURRENCE ON AN EA OR FONSI

The following applies to approval packages that require an Environmental Assessment (EA) and a Finding of No Significant Impact (FONSI):

A. Draft Approval Package:

The draft approval package requires a review by the Environmental Assessment Team (HFV-145). The Environmental Assessment Team

reviews the EA and FONSI section of the approval package for accuracy and completeness.

B. Final Approval Package:
The final approval package must be sent to HFV-145 for final concurrence if:

- any changes are made to the labeling with regard to environmental concerns or EA during or since the draft approval process,
- changes were requested during the draft approval process, or
- the approval will result in a change to the EA or FONSI.

NOTE: If the submission has received a categorical exclusion from the preparation of an EA, the approval package does not require Environmental Assessment Team (HFV-145) review. Such a package, when forwarded for standard quality assurance review in HFV-102, will be examined to verify that the grounds for granting the categorical exclusion are appropriate and adequately documented.

XI. ROUTING A REQUEST FOR A CURRENT GOOD MANUFACTURING PRACTICE (cGMP) STATUS CHECK

A cGMP status check of manufacturing and testing facilities cited in a submission is part of the Chemistry, Manufacturing, and Controls (CMC) review of that submission. In order for the submission to be approvable, the cGMP status of these facilities should be satisfactory.

If an approval letter is to be issued **immediately** following completion of a CMC review with a recommendation of "approvable," an additional status check by the primary reviewer is not necessary. However, if the approval letter is issued at a later date, the primary reviewer should assure that the cGMP status remains acceptable prior to issuing the approval letter. The primary reviewer can initiate a cGMP status check by forwarding a request to the CMC reviewer of the application. The CMC reviewer will verify the cGMP status of the appropriate

facilities and inform the primary reviewer. If the cGMP status remains satisfactory, the approval letter may be issued.

XII. ROUTING A REQUEST FOR A LABELING REVIEW

A copy of complete labeling for an NADA or a supplement to an NADA is sent to Division of Surveillance, Office of Surveillance and Compliance (HFV-210) for a review of labeling early in the review process. For Type A medicated articles and Type B and C medicated feeds, the labeling is also sent to the Medicated Feeds Team (HFV-226) in the Division of Animal Feeds (HFV-220).

A. The primary reviewer sends a request for a labeling review to HFV-210 for all original NADAs and supplemental NADAs that provide for the following:

   - New chemical entities (including new salts)
   - Novel formulations of currently approved drug substances
   - New routes of administration (with respect to a particular drug substance)
   - New species

B. The labeling for Type A medicated articles and/or Type B and C medicated feeds is sent to the Medicated Feeds Team (HFV-226) in the Division of Animal Feeds. Copies of all submitted labeling are sent with the request.

C. The labeling for any other NADAs or supplements may be sent for review at the discretion of the reviewer or team leader. Copies of all submitted labeling are sent with the request.

XIII. ROUTING A REQUEST FOR A BIORESEARCH MONITORING STATUS CHECK

A reviewer should obtain a Bioresearch Monitoring Status Check by sending the appropriate information to the Bioresearch Monitoring and Administrative Action Team (HFV-234), including the establishment (laboratory) name and location. Refer to CVM P&P Guide 1243.8220.

XIV. DER STATUS CHECK PROCESS

The primary reviewer makes a check of the Drug Experience Report records for an NADA in the Division of Surveillance (HFV-210) using the Oracle database prior to recommending approval. Selecting the Start button on the Windows desktop accesses the database. Press Start; Select Programs; Select Oracle; Select STARS; enter your user ID and password; select DER reports and from there select Drug Experience Reporting history. If the information needed is not there or the reviewer requires an explanation of the information in the database, the reviewer may obtain the necessary information via an email, a visit, or a telephone call to HFV-210.

XV. REFERENCES

CVM P& P Guide 1240.3000, New Animal Drugs for Investigational Use

CVM P & P Guide 1240.3100, Initial Processing of an NADA

CVM P & P Guide 1240.3110, Consulting Review of NADAs

CVM P & P Guide 1240.3125, Preparation Of A Draft Federal Register Notice Of Approval of a New Animal Drug Application (FR Notice)

CVM P & P Guide 1243.2580, Submission Document and Tracking

CVM P & P Guide 1243.7220, Environmental Review: Evaluating Claims of Categorical Exclusion for Actions Relating to New Animal Drugs

CVM P&P Guide 1243.8220, BIMO Inspection Request Process

New Animal Drug Application Form 356V

21 CFR 25.24; § 510.600, § 514.1; § 558.4

FDA Compliance Program Guidance Manual 7368.001, Pre-Approval Inspections: New Animal Drug Applications (NADA), Abbreviated New Animal Drug Applications (ANADA), Investigational New Animal Drug Applications (INAD)